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(71) Applicant (for all designated States except US):  
**NEWRON PHARMACEUTICALS SPA [IT/IT]**  
Via L. Ariosto, 21, I-20091 Bresso (MI) (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SALVATI, Patricia [IT/IT]**; Via Valera, 16/C, I-20020 Arese (IT). **VERNERONI, Orietta [IT/IT]**; Via Novara, 5, I-20147 Milan (IT). **MAJ, Roberto [IT/IT]**; Via Srafavia, 7, I-21047 Saronno (Va) (IT). **FARIELLO, Ruggero [IT/IT]**; Via della Vittoria, 22, I-21016 Luino\_(Va) (IT). **BENATTI, Luca [IT/IT]**; Via della Repubblica, 43, I-20093 Cologno Monzese (MI) (IT).

(74) Agents: **MANCINI, Vincenzo et al.**; Ing. A. Giambrocono & C. s.r.l., Via Rosolino Pilo, 19/B, I-20129 Milan (IT).

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING GABAPENTIN OR AN ANALOGUE THEREOF AND AN  $\alpha$ -AMINOAMIDE AND ITS ANALGESIC USE

(57) Abstract: There is disclosed a pharmaceutical composition comprising gabapentin or an analogue thereof (pregabalin or tiagabine) and an  $\alpha$ -aminoamide and its analgesic use. A synergistic effect of the respective analgesic activities without concomitant increase of side effects was observed.

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PHARMACEUTICAL COMPOSITION COMPRISING GABAPENTIN OR AN ANALOGUE THEREOF AND AN  $\alpha$ -AMINOAMIDE AND ITS ANALGESIC USE

The present invention relates to a pharmaceutical composition comprising gabapentin or an analogue thereof and an  $\alpha$ -aminoamide and its analgesic use. More particularly, this invention is directed to a pharmaceutical composition comprising gabapentin or pregabalin or tiagabine, and an  $\alpha$ -aminoamide useful in the treatment of pain.

Pain is commonly alleviated by administering analgesic drugs which act to decrease the sensation of pain by elevating the pain threshold, and/or altering its perception.

Although a large number of pain syndromes are treated by available therapies, chronic neuropathic pain syndromes that follow peripheral nerve damage have been found to have a much reduced sensitivity to the two major classes of analgesics, opioids and non steroidal antiinflammatory drugs (NSAID).

In the search for alternative forms of treatment, anticonvulsants have emerged as possible pharmacological interventions (McQuay et al., "Anticonvulsant drug for the management of pain: a systematic review", Br. Med. J., 311: 1047, 1995).

Among the new generation of antiepileptic drugs (AED) used for the treatment of neuropathic pain, 1-(aminomethyl)cyclohexaneacetic acid, also known as gabapentin (hereinafter GBP), an aminoacid structurally related to  $\gamma$ -aminobutyric acid (hereinafter GABA), occupies a prominent position together with its structural analogues, such as pregabalin (Tremont et al., "Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy.", Drugs, 60 (5): 1029-52, 2000) and tiagabine (Field et al., "Evaluation of Gabapentin and S-(+)-3-Isobutylgaba in a rat model of postoperative pain", J. Pharmacol. Exp. Ther.; 282 (3): 1242-4, 1997) as to frequency and broadness of use.

It has been reported that GBP is active in various animal

models of pain, where it blocks the late tonic phase of nociception induced by formalin, reverses allodynia of rats with neuropathy induced by partial ligation of the sciatic nerve (Pan et al., "Gabapentin suppresses ectopic nerve 5 discharges and reverses allodynia in neuropathic rats", J. Pharmacol. Exp. Ther.; 288 (3): 1026-30, 1999), as well as clinically, where it alleviates neuropathic pain, diabetic neuropathy and postherpetic neuralgia (Rosner et al., "Gabapentin adjunctive therapy in neuropathic pain states", 10 Clin. J. Pain; 12 (1): 56-8, 1996).

However, GBP produces a cohort of side effects in patients such as ataxia, dyspnea, nausea and sedation which limits its usefulness (FDA approved labelling text, NDA 21-216, NDA 20-235/S-015, NDA 20-882/S-002, NDA 21-129/S-005; 15 Rowbotham et al., "Gabapentin for the treatment of postherpetic neuralgia. A randomized controlled trial", JAMA 280 (21): 1831-1836, 1998; Backonja et al., "Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. A randomized controlled trial", JAMA 20 280 (21): 1837-1842, 1998).

On this ground, it would be desirable to find other compounds with antinociceptive mechanism of action different from and/or complementary to the one of GBP or its analogues so that lower doses of GBP or its analogues could be used 25 limiting the known side effects, yet allowing maintenance of its analgesic properties or even better potentiating them.

Although GBP was developed as a structural GABA analogue, it does neither appear to have direct "GABA-ergic" action, nor does it affect GABA uptake or metabolism. To explain the 30 antihyperalgesic effect of GBP, preliminary evidence points to the possible effect of GBP on the voltage dependent Ca<sup>++</sup> channels by interaction with the  $\alpha/2-\delta$  subunit. Experimental evidence supports the involvement of Ca<sup>++</sup> channels in the pathophysiology of pain. Thus, the action of GBP on these 35 channels may be a significant contributor to its antinociceptive effect.

Anticonvulsant drugs such as gabapentin, have been combined with non-toxic blockers for the N-methyl-d-aspartate (NMDA) receptor. Such compositions have been described as useful in the treatment of neuropathic pain. For example, WO 5 98/07447 discloses the combination of a neuropathic pain alleviating amount of an anticonvulsant drug, including gabapentin, lamotrigine, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, 10 carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, benzodiazepine, phenacemide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethedione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan 15 or L-5-hydroxytryptophan and an anticonvulsant potentiating amount of a non-toxic blocker for the NMDA receptor. This reference, however, does not teach any synergistic effect of the disclosed compositions.

Anticonvulsant drugs combined with NSAIDs or narcotic analgesics have also been described as useful in the treatment of pain. WO 99/12537 discloses a composition of the anticonvulsant compounds gabapentin or pregabalin in combination with the NSAID naproxen or with narcotic analgesics. Combinations of anticonvulsants and other drugs 25 with opioid analgesics have been suggested (Donnadieu, S., et al., Pain Relief, Presse Medicale, 1998, 27/39, 2062-2069). These references, however, also do not teach any synergistic effect of the disclosed compositions.

Combinations of anticonvulsant drugs, including GBP, with 30 the centrally acting analgesic tramadol, i.e. (1R,2R or 1S,2S)-2-[(dimethylamino)methyl]-1-[3-methoxyphenyl]cyclohexanol are described in WO 01/13904.

WO 00/61188 discloses a pharmaceutical composition comprising a sodium channel blocker and gabapentin or 35 pregabalin or salts or combinations thereof; the composition is effective in treating, preventing or ameliorating chronic

pain or convulsions. Among the sodium channel blockers, a number of aminoamides are cited, for instance the ones disclosed in US 5,449,692 (WO 94/22809), WO 97/05102, US 5,446,066 (WO 94/22808) and US 5,236,957 (WO 90/14334), although a composition comprising them is never exemplified, whereas the synergistic antiallodynic effect of gabapentin and the sodium channel blocker 4-(4'-fluorophenoxy)benzaldehyde semicarbazone, in the Chung model of neuropathic pain in rats, is therein illustrated.

It is an object of the present invention to provide a composition comprising an  $\text{Na}^+$  channel blocker  $\alpha$ -aminoamide and GBP, or pregabalin or tiagabine, having improved properties for the therapy of pain.

It is also an object of the present invention to provide a composition comprising an  $\alpha$ -aminoamide and GBP, or pregabalin or tiagabine, wherein the combination of said compounds shows a synergistic effect, while using less of each of said compounds.

Further, the Applicant noticed that not all the sodium channel blockers active in a model of chronic pain are synergic to gabapentin.

It has now been found that only some known  $\alpha$ -aminoamides or a pharmaceutically acceptable derivative thereof, endowed with analgesic activity, combined with GBP or pregabalin or tiagabine, or a pharmaceutically acceptable derivative thereof, significantly potentiate the analgesic or antinociceptive properties of GBP (or pregabalin or tiagabine), surprisingly providing an actual synergistic effect in comparison with the respective activities, and therefore succeeding in dramatically limiting the side effects of GBP (or pregabalin or tiagabine) by allowing to reduce its pharmaceutically effective amount to an unexpectedly lower dosage.

The pharmaceutical composition of the present invention comprises a combination of an  $\alpha$ -aminoamide and GBP (or

pregabalin or tiagabine), wherein the  $\alpha$ -aminoamide and GBP (or pregabalin or tiagabine) are present in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio is from about 1:1 to about 30:1 or from about 1:1 to about 1:30; 5 preferably from about 1:1 to about 9:1 or from about 1:1 to about 1:9; most preferably from about 1:1 to about 3:1 or 1:1 to about 1:3.

According to a first aspect of the present invention, a pharmaceutical composition is provided comprising gabapentin, 10 or pregabalin or tiagabine or a pharmaceutically acceptable derivative thereof, and an  $\alpha$ -aminoamide selected from the group consisting of (S)-(+)-2-[4-(2-fluorobenzylloxy)benzylamino]propanamide (internal code: NW-1029), (R)-(-)-2-[4-benzylloxybenzylamino]-3-phenyl-N-15 methylpropanamide, (internal code: NW-1037) and (S)-(+)-2-[4-(3-fluorobenzylloxy)-benzylamino]-N-methyl-propanamide (internal code: NW-1043);

if the case, either as a single isomer, or as a mixture thereof, or a pharmaceutically acceptable derivative thereof; 20 wherein the  $\alpha$ -aminoamide and gabapentin or pregabalin or tiagabine or the pharmaceutically acceptable derivatives thereof, are present in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio ranges from about 1:1 to about 30:1 or from about 1:1 to about 1:30, respectively.

25 Preferably, the above defined  $\alpha$ -aminoamide and GBP (or pregabalin or tiagabine) comprised in the pharmaceutical composition of the present invention are present in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio ranges from about 1:1 to about 9:1 or from about 1:1 to about 1:9, respectively; most preferably the ratio ranges from about 1:1 to about 3:1 or 1:1 to about 1:3, respectively.

30 A second aspect of the invention concerns the use of the above defined pharmaceutical composition for the preparation 35 of a medicament for the treatment of a condition of pain.

A further aspect of this invention relates to a method for treating a condition of pain in a mammal, including humans, in need thereof comprising administering to the mammal a therapeutically effective dose of the above defined pharmaceutical composition.

Particularly, the mammal in need of the said treatment is administered a dose of the pharmaceutical composition which ranges from about 0.05 to about 50 mg/die per kg of body weight; the pharmaceutical composition comprises gabapentin and an  $\alpha$ -aminoamide selected from the group consisting of (S)-(+)-2-[4-(2-fluorobenzyl)benzylamino] propanamide, (R)-(-)-2-[4-benzylbenzylamino]-3-phenyl-N-methylpropanamide, and (S)-(+)-2-[4-(3-fluorobenzyl)benzylamino]-N-methyl-propanamide, if the case, either as a single isomer, or as a mixture thereof, or a pharmaceutically acceptable derivative thereof, in a ratio of gabapentin and the  $\alpha$ -aminoamide, based on a fraction of their respective ED<sub>50</sub> values, of from about 1:1 to about 30:1 or from about 1:1 to about 1:30, more preferably of from about 1:1 to about 9:1 or from about 1:1 to about 1:9, most preferably of from about 1:1 to about 3:1 or from about 1:1 to about 1:3.

Neuropathic and chronic pain conditions in a mammal, including humans, can thus be alleviated and treated. Examples of conditions of mammalian pain which can be treated by the composition of the invention include centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain and neuropathic pain states, all of which would include acute pain such as caused by acute injury, trauma or surgery;

In particular, examples of pain conditions that can be treated by the composition of the invention include peripheral neuropathies, such as trigeminal neuralgia, post-herpetic neuralgia, diabetic neuropathy, or other metabolic neuropathies, glossopharyngeal neuralgia, radiculopathy, dental pain, cluster, migraine and any of the type of vascular headaches and neuropathy secondary to metastatic

infiltration, adiposis dolorosa and burn pain; central pain conditions following stroke, injury accidental or surgically or otherwise produced thalamic lesions and multiple sclerosis. Examples of pain inflammatory conditions that can 5 be treated by the composition of the invention include rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis, tendinitis and acute gouty arthritis.

"Treatment" as used herein covers any treatment of a condition in a mammal, particularly a human, and includes:

- 10 (i) preventing the disease from occurring in a subject which may be predisposed to the disease, but has not yet been diagnosed as having it;
- (ii) inhibiting the condition, i.e., arresting its development; or
- 15 (iii) relieving the condition, i.e., causing regression of the disease.

Both GBP (or pregabalin or tiagabine) and said  $\alpha$ -aminoamides and the pharmaceutically acceptable derivatives thereof are referred in the present description as the 20 "active compounds".

Further, a "pharmaceutically acceptable derivative" of the active compounds is herein meant to include any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, i.e. a compound which has a structural formula 25 different from the one of the active compounds and yet is directly or indirectly converted *in vivo* into a compound having their structural formula, upon administration to a mammal, particularly a human being.

Examples of pharmaceutically acceptable derivatives of 30 the active compounds include acid addition salts with inorganic acids, e.g. nitric, hydrochloric, hydrobromic, sulfuric, perchloric and phosphoric acids and the like, or organic acids, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, tartaric, citric, succinic, benzoic, 35 cinnamic, mandelic, methanesulfonic, p-toluenesulfonic and salicylic acids and the like.

The  $\alpha$ -aminoamides comprised in the composition of the invention and the analgesic activity thereof, in particular against chronic and neuropathic pain in mammals including humans, are disclosed in WO 90/14334 and WO 99/35125, respectively, and can be prepared according to what therein disclosed, said documents being herein incorporated by reference as far as the obtainment of said  $\alpha$ -aminoamides is concerned.

In a pharmaceutical composition of the present invention,  
10 an  $\alpha$ -aminoamide, GBP (or pregabalin or tiagabine), are  
present in a ratio based on a fraction of their respective  
ED<sub>50</sub> values which ratio may vary from about 1:1 to about 30:1  
or, reversibly, from about 1:1 to about 1 :30; preferably,  
from about 1:1 to about 9:1 or from about 1:1 to about 1:9;  
15 and, more preferably, from about 1:1 to about 3:1 or from  
about 1:1 to about 1 :3, depending upon the desired result.

The expert in the field will understand that, although GBP is preferably employed as one of the active compounds of the composition according to this invention, pregabalin or tiagabine may by used instead of GBP in said composition by applying the same concepts and ideas which form the basis of this invention.

The composition of the invention can be prepared by conventional procedures known in the art, for instance by mixing the active compounds with pharmaceutically, therapeutically inert organic and/or inorganic carrier materials. The composition of the invention can be in liquid form, e.g. in the form of a solution, suspension, emulsion; or in solid form, e.g. tablets, troches, capsules.

Suitable pharmaceutically, therapeutically inert organic and/or inorganic carrier materials useful in the preparation of the composition of the present invention include, for example, water, gelatin, gum arabic, lactose, starch, cellulose, magnesium stearate, talc, vegetable oils polyalkyleneglycols and the like. The pharmaceutical

composition of the invention can be sterilized and may contain further components, well known to the skilled in the art, such as, for example, preservatives, stabilizers, wetting or emulsifying agents, e.g. paraffin oil, mannide monooleate, salts to adjust osmotic pressure, buffers and the like.

The pharmaceutical composition of the invention is generally in the form of a dose unit.

Optimal therapeutically effective doses to be administered may be readily determined by those skilled in the art and will vary with the particular combination of an α-aminoamide and GBP (or pregabalin or tiagabine), with the amount of active ingredients used in a synergistic ratio based on a fraction of their respective ED<sub>50</sub> values, with the strength of the preparation, with the mode of administration and with the advancement of the condition or disorder treated. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutically effective level.

In general, a dose unit of the pharmaceutical composition of the invention may contain about 0.2 to 99.8, preferably about 0.5 to 99.5 percent by weight of each of the active compounds, in the whole mixture of the active compounds. The combination of the two active compounds, in general, can be administered to a mammal in need thereof in a wide range of dose from about 0.05 to about 50 mg/die per kg of body weight or, more specifically, to a human patient of an average body weight of 70 kg, in a dose of from about 3.5 mg to about 3500 mg/die.

Further, it is also within the scope of the invention to administer each active compound of the composition of the invention individually. Thus, it is also possible to formulate each of the two active compounds into separate dosage forms, in accordance with conventional procedures known in the art, and to administer them either

simultaneously or sequentially.

In other words, the unexpected analgesic activity obtained by the composition of the invention may be achieved by either simultaneous or sequential administration of the 5 active compounds.

Routes of administration of the composition of the invention may be both oral and parenteral. The composition should be administered at least once a day or more frequently, if needed, in relation to the severity of the 10 conditions of the patient. The analgesic effect observed is significantly greater than that which would result from the additive effect of the separate active compounds. The advantages of the antinociceptive potentiation are many, and include a reduction in the dosage of the GBP or pregabalin or 15 tiagabine required to produce analgesia, with a consequent reduction in undesirable side effects.

A single dose of a formulation of a pharmaceutical composition of the invention showing a synergistic activity, therefore, contains a therapeutically effective dose of 20 active ingredient which generally ranges from about 3.5 mg to about 3500 mg of a combination of an  $\alpha$ -aminoamide and GBP (or pregabalin or tiagabine); preferably, from about 8 mg to about 400 mg; more preferably, from about 15 mg to about 250 mg; and, most preferably, from about 18 g to about 90 mg. For 25 example, a 20 mg formulation of a pharmaceutical composition comprising GBP ( $ED_{50} = 12.40$  mg) and NW-1029 ( $ED_{50} = 0.82$  mg), in a 1:3 ratio, respectively, based on a fraction of their respective  $ED_{50}$  values, will contain about 16.7 mg of GBP and about 3.3 mg of NW-1029.

### 30 GENERAL METHODS

Co-administration of equipotent anti-nociceptive doses of different of the above defined  $\alpha$ -aminoamides (in particular NW-1029, NW-1037 and NW-1043) and of GBP was investigated in order to show that the composition of the invention produces 35 a synergistic effect greater than the activity shown by each of the active compounds when given alone, and greater than

the one that one would expect under simple additivity of the activities of each of the active compounds, without concomitant increase in related side effects. As previously recalled, typical side effects of GBP in animals are motor  
5 impairment and ataxia.

The synergistic antiallodynic effect of the composition of the invention and its effect on motor performance were evaluated using the following methods in the rat:

The testing for synergism of the active compounds of the  
10 composition of the invention was carried out according to the approach developed by Tallarida, R.J. 1992, Pain, 49: 93-97; Tallarida, R.J. et al. 1997, Life Sciences, Vol. 61, n. 26, 417-425; Przesmycki, K. et al. 1997, Eur. J. of Pharmacology, 337: 11-17.

This procedure involves the determination of the total amount in the mixture that is required to produce a specified synergistic antiallodynic effect at the 50% dose level (ED<sub>50mix</sub>) and the corresponding total amount that would be expected under simple additivity (ED<sub>50add</sub>). Where it is  
15 established that ED<sub>50mix</sub> < ED<sub>50add</sub> for a specific fixed ratio, then the composition has a synergistic antiallodynic effect. Both the quantities ED<sub>50mix</sub> and ED<sub>50add</sub> are random variables. ED<sub>50mix</sub> was determined from the dose-response curve for a specific fixed ratio of the components; ED<sub>50add</sub> was calculated  
20 from the ED<sub>50</sub> values for the individual drugs.  
25

ED<sub>50mix</sub> was then statistically compared to ED<sub>50add</sub>: in the present description, "significantly lower than the theoretical additive value" (ED<sub>50add</sub>) is meant to indicate the experimental ED<sub>50</sub> value is outside of the 95% Confidence  
30 Intervals (CI) of the ED<sub>50add</sub>.

In other words, if the actual ED<sub>50mix</sub> falls within the C.I. of the theoretical additive ED<sub>50add</sub>, the effect of the composition would be additive; otherwise, if the composition ED<sub>50mix</sub> is less than the theoretical additive ED<sub>50add</sub> (i.e. it  
35 does not fall within the theoretical C.I.), a significant synergistic interaction between the active compounds occurs.

Therefore, ED<sub>50</sub> values where considered to differ significantly (P< 0.05) from each other, if each ED<sub>50</sub> value was outside the 95% C.I. of the other.

GENERAL METHOD A:

5 Procedure for testing the antiallodynic effect of the composition of the invention

The procedure used to detect and compare the synergistic effect of the composition of the present invention for which there is a good correlation with human efficacy for the 10 treatment of pain is the procedure for the measurement of allodynia found in the monoarthritic rat model of chronic pain induced by complete Freund's adjuvant (CFA) (Butler et al., "A limited arthritic model for chronic pain studies in the rat" Pain; 48: 73-81, 1992).

15 Animals

Adult male Wistar rats (body weight 175-200 g, Harlan-Nossan, Italy) were housed in separate cages with free access to water and standard rat chow at a constant temperature (22±0.5°C) and relative humidity (60-70%), with a 6.00 am to 20 6.00 pm light-dark period.

Monoarthritic model

The inflammation was induced in rats by an intra-plantar injection of complete Freund's adjuvant (CFA, Sigma- 100 µl) into left hind paw containing heat-killed and dried 25 *Mycobacterium tuberculosis* in a mixture of paraffin oil and mannide monooleate as emulsifying agent. A group of control animal were injected with 100 µl of mineral oil, the incomplete Freund's adjuvant (IFA, Sigma). The CFA injection produced an area of localized edema and inflammation starting 30 48 h after injection, with a progressive reduction of the mechanical withdrawal threshold.

Each animal was allowed to develop the arthritis over an 8-9 day period of before testing.

Measurement of Mechanical Allodynia

35 Rats were placed in individual plastic boxes on a mesh

metal floor and allowed to acclimatize for about 30 min. A series of calibrated von Frey hair with logarithmically incremental stiffness (from 2.83 to  $5.88 \times \log_{10}$  of the bending force, g) were applied to the paw with the up-down method. Each hair was presented perpendicularly against the paw, with sufficient force to cause slight bending, and held approximately 2-3 sec. The filament was recorded when a positive response was noted (paw withdrawn, licking or shaking).

10 The antiallodynic effect was expressed as %MPE (Maximal Possible Effect) at 2 h post-dosing.

#### Animal Dosing

The rats were all dosed orally with various doses of an  $\alpha$ -aminoamide alone, GBP alone, combined doses of an  $\alpha$ -aminoamide and GBP or vehicle. The dosing volume was 2 ml/kg. The dosing materials were all prepared in the vehicle, (distilled water); drug weights were calculated as the free base. For the composition of the invention, the  $\alpha$ -aminoamide and GBP (or pregabalin or tiagabine) were both weighted as free base in the chosen ratio of their respective ED<sub>50</sub> and then dissolved in the appropriate volume to give the final dosing suspension.

#### Analysis of Antiallodynic Effect

Data are presented as mean of 4/6 animals per group/dose.

25 Multiple (typically 4) doses of each compound alone were studied for determining the ED<sub>50</sub>. The ED<sub>50</sub> was defined as the dose producing 50% reversal of mechanical hyperalgesia at 2h after treatment. An experimental ED<sub>50</sub> and 95% confidence intervals (CI) were calculated for each compound alone from 30 the linear regressions fitting the experimental data according to the equation  $y = a + bx$ .

The different  $\alpha$ -aminoamides were then combined with GBP at different ratios in relation to their respective ED<sub>50</sub> previously calculated (not limiting examples of the ratios 35 are 1:1; 1:3; 1:9 and respectively 1:1, 3:1 and 9:1 ratios)

for the evaluation of the synergic effect.

Multiple (typically 4) doses of each selected ratio were then studied orally for evaluating the synergic effect of the combination.

5      Each rat received only one treatment.

GENERAL METHOD B:

Rat Rotarod test

The Rotarod test is an established method used as predictive of CNS -related side effects in humans, and in  
10 particular motor impairment and ataxia.

Neurological deficit was indicated by the inability of the animal to remain on the rolling apparatus for the entire test time (J. Of the American Pharmaceutical Association, 1957, 46(3).208-209).

15      Multiple (typically 4-5) doses of each compound alone were studied for determining the TD<sub>50</sub> i.e. the dose of the tested compound causing 50% of the animals to fall from the roller, calculated by Probit analysis). The different  $\alpha$ -aminoamides were then combined with GBP at different ratios  
20 in relation to their respective TD<sub>50</sub> previously calculated (a non limiting example of the ratios is the 1:1 ratio) for the evaluation of the possible synergic effect. Data are presented as mean of 8/10 animals per group/dose.

The test was performed 120 min after drug administration.

25      RESULTS

By the test "von Frey" for the evaluation of antiallodynic activity, the mean baseline paw withdrawal threshold obtained for the naive control animals was 5.04±0.20 Log[10 x force (mg)]; in contrast, the mean rat  
30 withdrawal threshold of CFA-treated rats was significantly lower: 3.11±0.11 Log[10 x force (mg)]. Vehicle (distilled water) injection had no antihyperalgesic effect in the inflamed paws.

The  $\alpha$ -aminoamides given alone and in co-administration  
35 with GBP, were NW-1029, NW-1037, NW-1043. Groups were made of

4/6 animals.

All the compounds given alone produced a significant dose related antiallodynic effect, (reversing mechanical hypersensitivity) in inflamed paws.

5 The ED<sub>50</sub> estimated for GBP alone, 2 h after single administration was and 12.40 (C.I.: 10.3-14.3) mg/kg (Table 1).

10 The ED<sub>50</sub> estimated for NW 1029, NW-1037 and NW-1043 alone, 2 h after single administration, were 0.82 (C.I.: 0.2-4.1), 15 3.45 (C.I.: 2.3-4.7) and 7.05 (C.I.: 5.8-7.9) mg/kg, respectively (Table 1).

15 The ED<sub>50</sub> obtained experimentally (ED<sub>50mix</sub>) from the dose response curve after co-administration of NW-1029, NW-1037 and NW-1043 with GBP at fixed ratios are summarized in Table 1 as well and compared to the additive ED<sub>50add</sub>. The last column of Table 1 reports the calculated amounts of each ingredient of the composition in the experimental ED<sub>50mix</sub>.

20 The experimental values of ED<sub>50mix</sub> obtained for the NW-1029/GBP composition of the invention were lower than the calculated additive ED<sub>50add</sub> for all fixed dose ratios of drugs (see Table 1). Similar data were obtained for the others two compounds NW-1037 and NW-1043 in combination with GBP at the fixed dose ratio of 1:1.

25 The simultaneous administration of GBP and the active  $\alpha$ -aminoamides above defined produces an antinociceptive effect in an animal model of hyperalgesia, which is super-additive.

30 On the contrary, the effects obtained on the motor functions and ataxia are not super-additive as shown by the results obtained in the Rotarod test (Table 2). In fact, the TD<sub>50</sub> values obtained with NW-1029 and GBP alone or in the composition of the invention at the 1:1 ratio, in relation to their own TD<sub>50</sub>, are 470, 430 and 480 mg/kg, respectively. Therefore, the data above reported and illustrated confirm 35 that the composition of the invention permits to administer a diminished dose of GBP (or pregabalin or tiagabine) to obtain an effective antinociceptive activity, and to lower its side

effects.

Table 1

	ED <sub>50</sub> and (CI) p.o. at 2 hours (mg/kg)		DRUG COMBINATION in the ED <sub>50</sub> mix (mg/kg)	
	ED <sub>50</sub> add (CI)	ED <sub>50</sub> mix (CI)	Test Drug	GBP
NW-1029		0.82 (0.2-4.1)		
NW-1037		3.45 (2.4-4.8)		
NW-1043		7.05 (5.8-7.9)		
GBP		12.40 (10.3-14.5)		
NW-1029:GBP (1:9)	11.24 (9.5-12.8)	5.65 (4.53-6.2)	0.041	5.61
NW-1029:GBP (1:3)	9.51 (9.0-11.2)	4.98 (2.5-6.9)	0.11	4.87
NW-1029:GBP (1:1)	6.62 (4.7-7.3)	3.12 (1.9-4.2)	0.19	2.92
NW-1029:GBP (3:1)	3.73 (1.9-4.8)	1.52 (0.8-1.7)	0.25	1.27
NW-1029:GBP (9:1)	1.98 (1.7-2.4)	1.20 (0.7-1.6)	0.44	0.75
NW-1037:GBP (1:1)	7.92 (6.5-8.7)	4.03 (2.7-5.8)	0.87	3.17
NW-1043:GBP (1:1)	9.72 (8.7-10.8)	7.76 (4.8-8.1)	2.81	4.95

5 ED<sub>50mix</sub> = experimentally estimated ED<sub>50</sub>; CI = 95% Confidence Intervals; ED<sub>50add</sub> = theoretically calculated ED<sub>50</sub> of additivity.

Table 2

	TD <sub>50</sub> p.o. at 2 hours (mg/kg)		DRUG COMBINATION in the TD <sub>50</sub> mix (mg/Kg)	
	TD <sub>50add</sub> (CI)	TD <sub>50</sub> mix (CI)	Test Drug	GBP
NW-1029		470		
GBP		430		
NW-1029:GBP (1:1)	450	480	250.6	229.4

10

TD<sub>50</sub> mix = experimentally estimated TD<sub>50</sub>; TD<sub>50</sub> add = theoretically calculated TD<sub>50</sub> of additivity.

The above reported data show that the composition of the

invention permits to administer a diminished dose of GBP in order to obtain an effective antinociceptive activity, while lowering, at the same time, the side effects thereof. The administration of the composition of the invention can be 5 therefore noted to produce an antinociceptive effect in the animal model of hyperalgesia, which is super-additive since the actual ED<sub>50mix</sub> values, of any of the exemplified composition of the invention, do not fall within the theoretical C.I. ranges.

10 Following the same experimental protocol above illustrated, the ED<sub>50</sub> of 4-(4'-fluoro-phenoxy)benzaldehyde semicarbazone, both alone and in combination with gabapentin, in a 1:1 ratio, according to the disclosure of WO 00/61188, was evaluated after oral treatment.

15 The values of the ED<sub>50</sub> for said semicarbazone alone (14.5 mg/kg - C.I.: 11.9-15.8) and in combination with gabapentin (13.2 mg/kg - C.I.: 12.1-15.3) were found non-significantly different.

20 In view of the foregoing, it can be therefore noted that not all the sodium channel blockers, active in a model of chronic pain, as shown by the comparative data above illustrated, are synergic to GBP, adversely to what inadvertently and significantly found out for the  $\alpha$ -aminoamides NW-1029, NW-1037 and NW-1043 comprised in the 25 composition of the invention.

The following illustrative examples of pharmaceutical compositions according to the invention are prepared by mixing the ingredients below listed, employing methods usual in the pharmaceutical field.

30 EXAMPLE 1 ( $\alpha$ -aminoamide:GBP ratio: 1:1)

A capsule contains:

NW-1029	13.3 mg
GBP	204.4 mg
Talc	5.7 mg
Corn starch	19.6 mg
Microcrystalline cellulose	52.0 mg
Magnesium stearate	5.0 mg

EXAMPLE 2 ( $\alpha$ -aminoamide:GBP ratio: 1:3)

A capsule contains:

NW-1029	7.7 mg
GBP	341.0 mg
Talc	5.3 mg
Corn starch	20.0 mg
Microcrystalline cellulose	23.0 mg
Magnesium stearate	3.0 mg

EXAMPLE 3 ( $\alpha$ -aminoamide:GBP ratio: 9:1)

A capsule contains:

NW-1029	31.0 mg
GBP	52.5 mg
Talc	3.5 mg
Corn starch	15.0 mg
Microcrystalline cellulose	45.0 mg
Magnesium stearate	3.0 mg

**CLAIMS**

1. A pharmaceutical composition comprising gabapentin, or pregabalin or tiagabine or a pharmaceutically acceptable derivative thereof and an  $\alpha$ -aminoamide selected from the group consisting of (S)-(+)-2-[4-(2-fluorobenzyl)benzylamino]propanamide, (R)-(-)-2-[4-benzylbenzylamino]-3-phenyl-N-methylpropanamide, and (S)-(+)-2-[4-(3-fluorobenzyl)benzylamino]-N-methylpropanamide, if the case, either as a single isomer or as a mixture thereof, or a pharmaceutically acceptable derivative thereof;

wherein the  $\alpha$ -aminoamide and gabapentin or pregabalin or tiagabine or the pharmaceutically acceptable derivatives thereof, are present in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio ranges from about 1:1 to about 30:1 or from about 1:1 to about 1:30, respectively.

2. A pharmaceutical composition according to claim 1, wherein the  $\alpha$ -aminoamide and gabapentin, or pregabalin or tiagabine, are in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio ranges from about 1:1 to about 9:1 or from about 1:1 to about 1:9, respectively.

3. A pharmaceutical composition according to claim 1 or 2, wherein the  $\alpha$ -aminoamide and gabapentin, or pregabalin or tiagabine, are in a ratio based on a fraction of their respective ED<sub>50</sub> values, which ratio ranges from about 1:1 to about 3:1 or 1:1 to about 1:3, respectively.

4. Use of a pharmaceutical composition according to any of the previous claims for the preparation of a medicament for the treatment of a condition of pain.

30 5. A method for treating a condition of pain in a mammal in need thereof comprising administering to the mammal a therapeutically effective dose of a pharmaceutical composition according to claims 1, 2 or 3.

35 6. A method according to the previous claim, wherein the mammal in need of the said treatment is administered a dose

of the pharmaceutical composition which ranges from about 0.05 to about 50 mg/die per kg of body weight.

7. A method according to claim 5 or 6, wherein the pharmaceutical composition comprises gabapentin and the  $\alpha$ -aminoamide, in a ratio based on a fraction of their respective ED<sub>50</sub> values, of from about 1:1 to about 30:1 or from about 1:1 to about 1:30, respectively.

8. A method according to any of claims 5 to 7, wherein gabapentin and the  $\alpha$ -aminoamide are in a ratio, based on a fraction of their respective ED<sub>50</sub> values, of from about 1:1 to about 9:1 or from about 1:1 to about 1:9.

9. A method according to any of claims 5 to 8, wherein gabapentin and the  $\alpha$ -aminoamide are in a ratio, based on a fraction of their respective ED<sub>50</sub> values, of from about 1:1 to about 3:1 or from about 1:1 to about 1:3.

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**WO 03/020273 A3**

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- (71) Applicant (for all designated States except US):  
**NEWRON PHARMACEUTICALS SPA [IT/IT]**  
Via L. Ariosto, 21, I-20091 Bresso (MI) (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SALVATI, Patricia [IT/IT]**; Via Valera, 16/C, I-20020 Arese (IT). **VERONI, Orietta [IT/IT]**; Via Novara, 5, I-20147 Milan (IT). **MAJ, Roberto [IT/IT]**; Via Srafavia, 7, I-21047 Saronno\_(Va) (IT). **FARIELLO, Ruggero [IT/IT]**; Via della Vittoria, 22, I-21016 Luino\_(Va) (IT). **BENATTI, Luca [IT/IT]**; Via della Repubblica, 43, I-20093 Cologno Monzese (MI) (IT).
- (74) Agents: **MANCINI, Vincenzo et al.**; Ing. A. Giambrocono & C. s.r.l., Via Rosolino Pilo, 19/B, I-20129 Milan (IT).
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WO 03/020273 A3

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING GABAPENTIN OR AN ANALOGUE THEREOF AND AN  $\alpha$ -AMINOAMIDE AND ITS ANALGESIC USE

(57) Abstract: There is disclosed a pharmaceutical composition comprising gabapentin or an analogue thereof (pregabalin or tiagabine) and an  $\alpha$ -aminoamide and its analgesic use. A synergistic effect of the respective analgesic activities without concomitant increase of side effects was observed.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/08910

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P29/00 A61P25/08 A61K31/445 A61K31/195 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 61188 A (COCENSYS INC) 19 October 2000 (2000-10-19) page 3, line 24 -page 4, line 17; claims 1-5, 9-14 page 10-18 page 21, line 7-26 ----	1-9
Y	WO 98 19674 A (BENDTSEN LARS ; JENSEN RIGMOR (DK); MADSEN ULF (DK); OLESEN JES (DK) 14 May 1998 (1998-05-14) page 30-37; claims 14, 17, 26, 44, 47-50; example 6 ----	1-9
Y	WO 01 45684 A (GLAXO GROUP LTD) 28 June 2001 (2001-06-28) page 20, line 14, paragraph 2; claims 1, 4 ----	1-9 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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# **INTERNATIONAL SEARCH REPORT**

## **International Application No.**

PCT/EP 02/08910

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 53225 A (WARNER LAMBERT CO) 14 September 2000 (2000-09-14) page 1, line 20,21; claims 1-5,13-15 page 5, line 20-25 page 2, line 14-25 ---	1-9
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A	WO 99 35125 A (NEWRON PHARM SPA) 15 July 1999 (1999-07-15) cited in the application the whole document ---	1,4,5,7
A	WO 99 35123 A (NEWRON PHARM SPA) 15 July 1999 (1999-07-15) cited in the application the whole document ---	1,4,5,7
A	WO 98 03167 A (WARNER LAMBERT CO) 29 January 1998 (1998-01-29) page 13, line 10-16; claims 1,4-15 ---	1,4,5,7
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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims searched incompletely: 1-9.

Present claims 1-9 relate to compositions, uses and methods involving potentially an extremely large number of possible compounds by way of the term "derivative" in claim 1. Due thereto, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the complete scope of the claims impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely to the compounds (specifically) mentioned in the claims and examples, with due regard being given to the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## **INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/EP 02/08910

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims (under Article 17(2)(a)) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5–9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
  2.  Claims Nos.: — because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
  3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: \_\_\_\_\_
  4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: \_\_\_\_\_

## **Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.
  - No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/08910

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Information on patent family members

International Application No

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